International Journal of Gerontology 17 (2023) 295–298
https://doi.org/10.6890/IJGE.202310_17(4).0016

International Journal of Gerontology

journal homepage: http://www.sgecm.org.tw/ijge/

Case Report

Mucormycosis Treated with Isavuconazole as an Oral Replacement Therapy in a 65-Year-Old Diabetic Patient with Acute Liver Injury

Hsiang-Ling Lin [a *], Chang-Pan Liu [a,b,c], Hsun Chang [a]

[a] *Division of Infectious Diseases, Department of Internal Medicine, MacKay Memorial Hospital, Taipei, Taiwan,* [b] *Department of Medicine, MacKay Medical College, New Taipei City, Taiwan,* [c] *Committee of Infection Control, MacKay Memorial Hospital, Taipei, Taiwan*

ARTICLE INFO

Accepted 1 March 2023

Keywords:
drug-induced liver injury,
isavuconazole,
mucormycosis,
posaconazole

SUMMARY

Mucormycosis, also known as black fungus, is a rare fungal infection that has high morbidity and mortality even with early diagnosis and treatment. Hematological malignancy, trauma, and poorly-controlled diabetes mellitus are known risk factors for mucormycosis. Rhino-orbito-cerebral mucormycosis is the most common clinical presentation, and amphotericin B and posaconazole are often used for mucormycosis treatment. Posaconazole has been associated with acute drug induced liver injury in some cases. Hence, isavuconazole is an alternative choice. We present a case of rhino mucormycosis in a 65-year-old man with uncontrolled diabetes mellitus. He developed acute liver injury after posaconazole exposure and was subsequently treated successfully with isavuconazole.

1. Introduction

Mucormycosis is a rare invasive fungal infection.

Hematological malignancy, solid organ transplant, trauma, prolonged steroid use and poorly-controlled diabetes mellitus are known risk factors, with poorly-controlled diabetes mellitus a predominant risk factor in Asia.[1,2]

The global incidence of mucormycosis varies from 0.005 to 1.7 per million in the population, with India reporting to have the highest estimated incidence of mucormycosis.[3] In comparison with pulmonary mucormycosis, cutaneous mucormycosis and disseminated mucormycosis, rhino-orbito-cerebral mucormycosis is the most common, especially in diabetic patients. Cutaneous mucormycosis has a lower mortality rate and mostly affects trauma patients. Disseminated mucormycosis is a fatal disease in patients with hematological malignancy.

In terms of treatment, liposomal amphotericin B is recommended as first-line therapy for mucormycosis. Surgical debridement and correcting the underlying disease and risk factors are also important aspects of treatment.[4]

2. Case presentation

A 65-year-old man with hypertension, chronic obstructive pulmonary disease (COPD), and uncontrolled diabetes mellitus presented to our clinic. He suffered from nasal obstruction with odorous smelling for two weeks. These symptoms worsened with headaches, left cheek pain, and left periorbital swelling sensations that developed three days before admission. Occasional epistaxis was also reported, but he had no fever, diplopia, or visual field defects.

He visited our otolaryngology outpatient department, where sinoscopy showed a blackish curst over the bilateral middle turbinates and nasal septum (Figure 1).

A Water's view X-ray of the skull showed an air-fluid level and coarse mucoperiosteal membranes of the left maxillary sinus. A paranasal sinus computer tomography scan (CT) showed that the nasal septum was deviated to the right side, there was mucosal thickening of the left ethmoid sinus, and there was an air-fluid level with central high density in the left maxillary sinus (Figure 2). There was an impression of rhinosinusitis .

The patient was admitted and underwent left endoscopic sinus surgery and debridement. Pathology and histopathology examinations with periodic acid-Schiff (PAS) and Grocott methenamine-silver (GMS) stains showed mixed fungal microorganisms with thick and pauci-septate hyphae as well as some spores.

These findings are compatible with a diagnosis of mucormycosis (Figure 3).

Further evaluations, including brain and chest CT, were arranged to assess central nervous system and lung mucormycosis. There was no evidence of brain lesions or pulmonary mucormycosis. A fungus culture from a nose sample showed a Rhizopus species.

In addition to surgical debridement, antifungal treatment with liposomal amphotericin B (350 mg/day) was administered. The patient underwent endoscopic debridement repeatedly since there was a lot of fungal debris noted in endoscopy examinations, which were performed every week. After the initiation of antifungal medication for three weeks, a follow-up sinoscopy showed fair improvement with only mild eschar over the left lamina papyracea and anterior end of the nasal septum. However, the patient could not tolerate hospitalization and asked to be discharged, even though it was against medical advice. He was discharged with directions for oral

* Corresponding author. Division of Infectious Diseases, Department of Internal Medicine, MacKay Memorial Hospital, Taipei, Taiwan.
E-mail address: cutebagel@hotmail.com (H.-L. Lin)

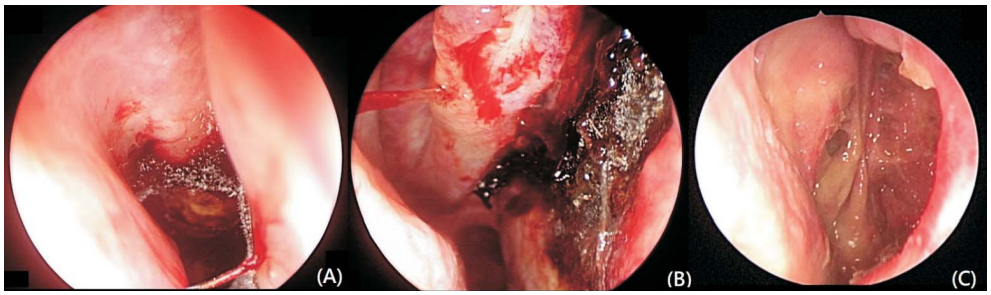

Figure 1. (A) Appearance of mucosal fungal growth with blackish crust. (B) Blackish crust over the bilateral middle turbinates and nasal septum under sinoscopy in the left nostril. (C) No more blackish crust in the left nostril observed at outpatient follow-up after treatment.

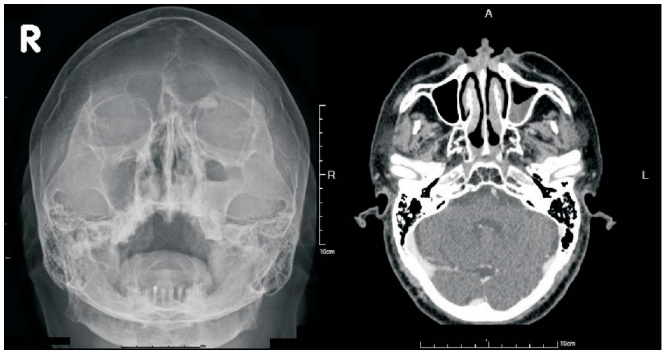

Figure 2. Computer tomography and Water's view X-ray of the skull showed an air-fluid level in the left maxillary sinus with mucosal thickening, indicating sinusitis.

posaconazole treatment (200 mg/day) and outpatient department follow-up was arranged.

However, malaise and poor appetite was noted for one week after discharge. Sinoscopy in the outpatient department showed a left ostiomeatal complex crust and ischemic changes of the left frontal sinus. Magnetic resonance imaging revealed partial loss of the nasal septum. The patient was admitted again for further debridement due to local recurrence of mucormycosis and abnormal liver enzymes (alanine aminotransferase: 578 U/L, normal range 14–40 U/L) (Table 1), possibly due to adverse effects of posaconazole treatment.

After admission, antifungal treatment with liposomal amphotericin B (350 mg/day) were resumed. The symptoms malaise and raised liver enzymes improved after posaconazole was stopped.

Follow-up endoscopy showed fair improvement with only little eschar remaining over the left vidian canal after antifungal treatment for one month. The antifungal agent was changed to oral isavuconazole without obvious adverse effects. He was discharged with oral isavuconazole (200 mg/day) and followed up in the otolaryngology and infectious disease outpatient departments (Figure 1C).

After continuous treatment with oral isavuconazole for six months, an endoscopic biopsy showed no more fungal hyphae or spores under PAS and GMS staining. The patient was therefore treated successfully.

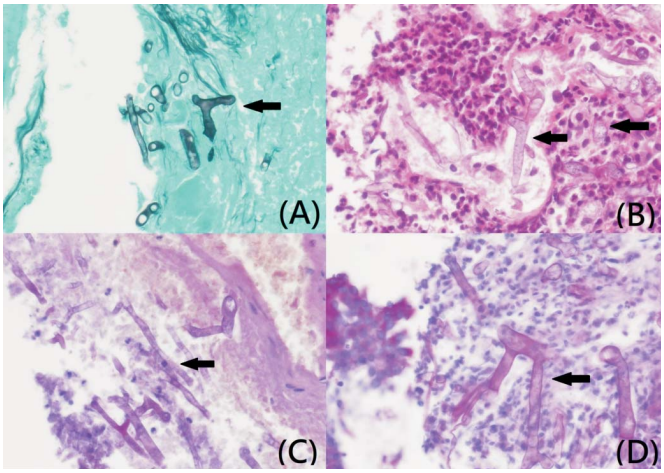

Figure 3. (A) Grocott methenamine-silver (GMS) stain. (B) Hematoxylin and eosin stain (H&E) stain. (C, D) Periodic acid-Schiff (PAS) stain. Mixed fungal microorganisms with dedicated or thick hyphae as well as some spores were found with PAS and GMS stains. PAS stain revealed thick and ribbon-like hyphae with fungal spores. The angle of branching usually approached 90°, which is compatible with mucormycosis (arrows).

3. Discussion

In Taiwan, the incidence of mucormycosis is 0.07 to per million in the population and the mortality rate is 39%, with most infected patients having diabetes mellitus.[5,6]

Mucormyosis is caused by mucorales, which are fungi that are ubiquitous in the environment. Rhizopus spp. is more often observed in patients with rhino-orbital-cerebral mucormycosis.[7]

Rhinocerebral mucormycosis was the most common clinical presentation (34%), followed by pulmonary mucormyosis (21%), cutaneous mucormyosis (20%), and disseminated mucormyosis (14%) in a review study by Jeong et al.[2]

Patients with an immunocompromised status, for example, hematological malignancy, solid organ transplantation, corticosteroid use, and diabetic mellitus, are at particular risk for developing mucormycosis.[1] Among these risk factors, diabetic mellitus was re-

Table 1
Antifungal treatment course and liver enzymes data indicating raised liver enzymes with clinical presentation of malaise noted after posaconazole use.

	Baseline	1st admission		Discharge	2nd admission			OPD	
		D0	D+7	D+24	D+30	D+41	D+64	D+91	D+133
GOT/AST (IU/L) (15–41 IU/L)	18	12	15	17	168*	102	106	54	20
GPT/ALT (IU/L) (14–40 IU/L)	41	–	29	29	578*	235	137	78	18
		Lipo-AB 350 mg/day		Posaconazole 300 mg/day		Lipo-AB 350 mg/day		Isavuconazole 200 mg/day	

OPD: outpatient department, Lipo-AB: liposomal amphotericin B.

ported to be an independent risk factor for rhino-orbital-cerebral mucormycosis.[7]

Steroid use is also known as a risk factor for mucormycosis. In the post COVID-19 era, there have been many studies on pulmonary mucormycosis in post COVID infections due to steroid use.[8,9]

Coincidentally, there have been some case reports of mucormycosis in COPD patients.

A case with COPD under oral steroid control developed pulmonary mucormycosis.[10] Another case developed rhino mucormycosis after a short course of high dose steroid therapy for acute exacerbation of COPD.[11] However, none of these cases mentioned corticosteroid inhaler use, and further studies may be warranted if corticosteroid inhaler use was suspected of increasing the risk of rhino mucormycosis in COPD patients.

Clinical symptoms of rhinocerebral mucormycosis mostly involve the head region. Common presentations include one-sided headaches, nasal congestion, a black and foul-smelling nasal discharge, and epistaxis.[12] Corzo-Leon et al. proposed an algorithm, that listed the signs and symptoms of possible rhinocerebral mucormycosis in diabetic patients, including cranial nerve palsy, diplopia, sinus pain, proptosis and periorbital swelling.[13]

Our patient, had the risk factor of diabetes mellitus without medical control. The initial presentation of headache, nasal congestion, and odorous smelling, subsequently progressed to occasional epistaxis and periorbital swelling, which are typical symptoms.

Early diagnosis and adequate management of mucormycosis are important. In addition to the use of antifungal agents, surgical debridement can be used to decrease mortality and treatment failure.

In a case series that enrolled 21 rhinocerebral mucormycosis cases in Kaohsiung, Taiwan, 15 of 16 surviving patients received both antifungal treatment and surgical debridement.[6] Nevertheless, a systemic review of rhinocerebral mucormycosis enrolled 345 cases also reported 1.5-fold increase in survival rates in patients who underwent debridement.[14]

Reversal or discontinuation of underlying predisposing factors is also recommended for successful treatment of mucormycosis.[15,16] Hyperglycemic control is strongly recommended by ESCMID and ECMM joint clinical guidelines for the diagnosis and management of mucormycosis.[17]

Our patient underwent several endoscopic debridement treatments and rechecks, antifungal treatment, and insulin injection for blood sugar control as soon as mucormycosis was diagnosed.

Amphotericin B and posaconazole are the medications used most often for mucormycosis. Triazole antifungals were known to have the potential hepatotoxicity, which may result in acute liver injury, ranges from asymptomatic abnormalities in liver function tests to fulminant hepatic failure.

Higher rates of acute liver injury were reported among users of posaconazole in a cohort study.[18] Additionally, longer treatment duration for fungal infections may be related to an increased risk of acute liver injury.

Isavuconazole is a new triazole for mucormycosis treatment, that was shown to be not inferior to amphotericin B in all-cause mortality.[19] Isavuconazole was shown to be effective primary and salvage therapies for mucormycosis in a single-arm open-label trial (VITAL study) published in 2016.[20]

Isavuconazole has many advantages including less hepatic toxicity, stable pharmacokinetics, and good oral bioavailability.[21]

A retrospective study by DiPippo, Adam J et al. enrolled 20 patients with leukemia who had adverse effects with liver toxicity on posaconazole. All patients tolerated subsequent isavuconazole treatment and acute liver injury improved after discontinued posaconazole.[22]

There have been similar cases that showed successful treatment for rhino mucromyosis in a poorly-controlled diabetic patient series under isavuconazole and surgical debridement. One of these patients also had acute liver injury after posaconazole exposure, and recovered well after changing to isavuconazole.[23]

In summary, we present a poorly-controlled diabetic patient with rhino mucormycosis who was successfully treated with isavuconazole after discontinuation of amphotericin B.

This case adds to the growing evidence for use of isavuconazole in mucormycosis treatment. Additionally, this case may improve physicians' awareness of mucormycosis in diabetic patients, which is a rare but fatal disease that needs early diagnosis and treatment.

Conflict of interest

The authors declare no conflict of interest regarding the publication of this paper.

References

1. Skiada A, Lass-Floerl C, Klimko N, Ibrahim A, Roilides E, Petrikkos G. Challenges in the diagnosis and treatment of mucormycosis. *Med Mycol.* 2018;56(suppl_1):93–101. doi:10.1093/mmy/myx101
2. Jeong W, Keighley C, Wolfe R, et al. Contemporary management and clinical outcomes of mucormycosis: A systematic review and meta-analysis of case reports. *Int J Antimicrob Agents.* 2019;53(5):589–597. doi:10.1016/j.ijantimicag.2019.01.002
3. Cornely A, Alastruey-Izquierdo A, Arenz D, et al. Global guideline for the diagnosis and management of mucormycosis: an initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium. *Lancet Infect Dis.* 2019;19(12):e405–e421. doi:10.1016/S1473-3099(19)30312-3
4. Pilmis B, Alanio A, Lortholary O, Lanternier F. Recent advances in the understanding and management of mucormycosis. *F1000Res*. 2018;7: F1000 Faculty Rev-1429. doi:10.12688/f1000research.15081.1
5. Shih HI, Huang YT, Wu CJ. Disease burden and demographic characteristics of mucormycosis: A nationwide population-based study in Taiwan, 2006-2017. *Mycoses*. 2022;65(11):1001–1009. doi:10.1111/myc.13484
6. Khor BS, Lee MH, Leu HS, Liu JW. Rhinocerebral mucormycosis in Taiwan. *J Microbiol Immunol Infect.* 2003;36(4):266–269.
7. Jeong W, Keighley C, Wolfe R, et al. The epidemiology and clinical manifestations of mucormycosis: a systematic review and meta-analysis of case reports. *Clin Microbiol Infect.* 2019;25(1):26–34. doi:10.1016/j.cmi.2018.07.011
8. Sengupta I, Nayak T. Coincidence or reality behind mucormycosis, diabetes mellitus and Covid-19 association: A systematic review. *J Mycol Med.* 2022;32(3):101257. doi:10.1016/j.mycmed.2022.101257
9. Zobairy H, Salem MM, Ghajarzadeh M, Mirmosayyeb O, Mirsalehi M. Diabetes mellitus and other underlying conditions in patients with coronavirus disease 2019 associated rhino-orbito-cerebral mucormycosis: a systematic review and meta-analysis. *J Laryngol Otol.* 2022;136(9):788–798. doi:10.1017/S0022215122001074
10. Spira A, Brecher S, Karlinsky J. Pulmonary mucormycosis in the setting of chronic obstructive pulmonary disease. A case report and review of the literature. *Respiration.* 2002;69(6):560–563. doi:10.1159/000066467
11. Ferguson AD. Rhinocerebral mucormycosis acquired after a short course of prednisone therapy. *J Am Osteopath Assoc.* 2007;107(11):491–493.
12. Bhandari J, Thada PK, Nagalli S. Rhinocerebral Mucormycosis. In: StatPearls. Treasure Island (FL): StatPearls Publishing; July 3, 2023.
13. Corzo-León DE, Chora-Hernández LD, Rodríguez-Zulueta AP, Walsh TJ. Diabetes mellitus as the major risk factor for mucormycosis in Mexico: Epidemiology, diagnosis, and outcomes of reported cases. *Med Mycol.* 2018;56(1):29–43. doi:10.1093/mmy/myx017
14. Salehi M, Mahmoudi S, Rezahosseini O, et al. The epidemiological, clinical, mycological, and pathological features of rhino-cerebral mucormycosis: A systematic review. *Iran J Pathol.* 2022;17(2):112–121. doi:10.30699/IJP.2022.538690.2721
15. Arendrup MC, Boekhout T, Akova M, et al. ESCMID and ECMM joint clinical guidelines for the diagnosis and management of rare invasive yeast

infections. *Clin Microbiol Infect.* 2014;20 Suppl 3:76–98. doi:10.1111/1469-0691.12360
16. Katragkou A, Walsh TJ, Roilides E. Why is mucormycosis more difficult to cure than more common mycoses? *Clin Microbiol Infect.* 2014;20 Suppl 6:74–81. doi:10.1111/1469-0691.12466
17. Cornely OA, Arikan-Akdagli S, Dannaoui E, et al. ESCMID and ECMM joint clinical guidelines for the diagnosis and management of mucormycosis 2013. *Clin Microbiol Infect.* 2014;20 Suppl 3:5–26. doi:10.1111/1469-0691.12371
18. Lo Re V 3rd, Carbonari DM, Lewis JD, et al. Oral azole antifungal medications and risk of acute liver injury, overall and by chronic liver disease status. *Am J Med.* 2016;129(3):283–291.e5. doi:10.1016/j.amjmed.2015.10.029
19. Jenks JD, Salzer HJ, Prattes J, Krause R, Buchheidt D, Hoenigl M. Spotlight on isavuconazole in the treatment of invasive aspergillosis and mucormycosis: design, development, and place in therapy. *Drug Des Devel Ther.* 2018;12:1033–1044. doi:10.2147/DDDT.S145545
20. Marty FM, Ostrosky-Zeichner L, Cornely OA, et al. Isavuconazole treatment for mucormycosis: a single-arm open-label trial and case-control analysis. *Lancet Infect Dis.* 2016;16(7):828–837. doi:10.1016/S1473-3099(16)00071-2
21. Ananda-Rajah MR, Kontoyiannis D. Isavuconazole: a new extended spectrum triazole for invasive mold diseases. *Future Microbiol.* 2015;10(5):693–708. doi:10.2217/fmb.15.34
22. DiPippo AJ, Rausch CR, Kontoyiannis DP. Tolerability of isavuconazole after posaconazole toxicity in leukaemia patients. *Mycoses.* 2019;62(1):81–86. doi:10.1111/myc.12851
23. Miller RP, Farrugia L, Leask J, Khalsa K, Khanna N, Melia L. Successful treatment of rhizopus arrhizus rhino-orbital-cerebral mucormycosis with isavuconazole salvage therapy following extensive debridement. *Med Mycol Case Rep.* 2021;32:39–42. doi:10.1016/j.mmcr.2021.03.005